

Use of octreotide for relief of gastro-intestinal (GI) symptoms in systemic mastocytosis

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CASE

We present the case of an 82-year-old Caucasian female who was evaluated by hematology oncology for further work up and management of her chronic but progressive anemia. She reported weight loss, poor appetite, fatigue, nausea, several episodes of non-bloody diarrhea and increased abdominal girth over the past 3 months. On admission, her hemoglobin was 8.9 gm/dL, platelets were 43 k/mcl, WBC was 5.49 K/mcl with absolute neutrophil count of 3.73 k/mcl and 0% peripheral blasts. Her metabolic panel was abnormal for elevated LDH (245 U/L) and alkaline phosphatase (207 U/L). Her liver function tests were normal except for albumin of 2.5 g/dl. Computed tomography (CT) of the abdomen/pelvis showed splenomegaly, ascites, and retroperitoneal lymphadenopathy, a concern for a lymphoproliferative or metastatic disease.

A bone marrow biopsy and aspirate performed to determine the cause of her progressive anemia and thrombocytopenia revealed hypercellularity (90%) and increased blasts (35% on the touch preparation). The blasts had scant cytoplasm and fine chromatin (blue arrows in Figure 1). In addition, there were paratrabecular infiltrates of round to spindled mast cells (red arrow in Figure 1), which by immunohistochemistry were strongly positive for tryptase (shown in Figure 2), CD117, CD68 and CD25. The blasts were weakly positive for CD117 and strongly positive for myeloperoxidase, CD56, Bcl-2, and CD43 (not shown). The aspirate was severely hemodiluted, likely due to the reticulin fibrosis observed in the biopsy. Flow cytometry specimen was also hemodiluted (9%

blasts) with the following myeloid immunophenotype: CD33 positive CD13 positive CD56 positive CD117 partially positive CD34 negative HLA-DR negative. Based on these findings the patient was diagnosed with AML and SM, a subset of systemic mastocytosis with associated clonal hematologic non-mast cell lineage disease (SM-AHNMD).

The patient's diarrhea responded briefly to antimotility agent loperamide, but while awaiting definitive treatment plan, her symptoms worsened rapidly and required admission for severe, profuse non-bloody diarrhea, dehydration and abdominal distension. Splenomegaly and ascites were noted on clinical exam. Labs continued to show anemia and thrombocytopenia. Initial test was positive for clostridium difficile (*C. diff*). This was successfully treated with metronidazole and then with oral vancomycin. Subsequent tests for *C. diff*, other infectious agents and transglutaminase IgA antibody were negative. However, the patient continued to have multiple episodes of diarrhea with little relief from antimotility agents. Diarrhea was deemed secondary to SM. Extensive work up for portal hypertension was non-diagnostic. She could not undergo colonoscopy and liver biopsy due to thrombocytopenia. As a consideration for treatment with imatinib she was tested for BCR/ABL and PDGFRA fusion genes which were negative. KIT mutation analysis could not be performed due to lack of tissue sample. After a lengthy discussion with the patient regarding various options of treatment, she chose palliative care and hospice. However, severe diarrhea limited her transition to hospice; she was then started on a trial of octreotide every 8 h for her diarrhea. She had a rapid response with dra-

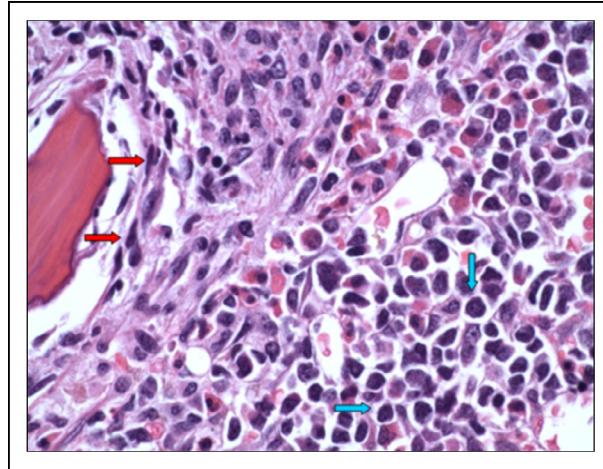


Figure 1. Hypercellular marrow with blasts (blue arrows) and paratrabecular infiltrates of mast cells (red arrows). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

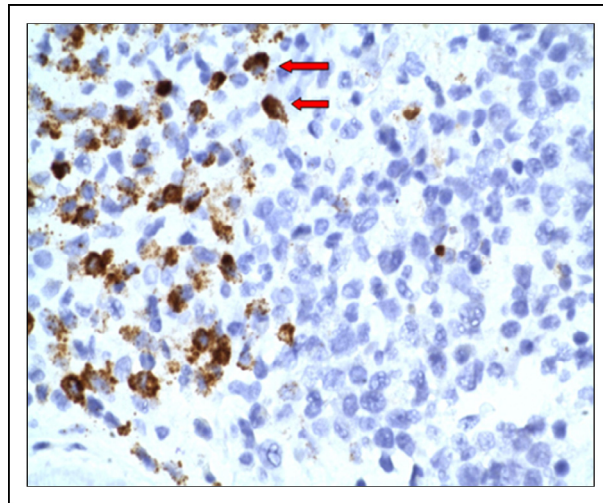


Figure 2. Intense staining by foci of mast cell infiltrates by tryptase (red arrows). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

matic improvement in her diarrhea symptoms and was appropriately transitioned to inpatient hospice care.

DISCUSSION

Diagnosis of SM cannot be based on clinical findings alone; therefore, bone marrow biopsy remains the cornerstone for confirming suspicion of the disease. One major and at least one minor criterion or three minor criteria must be satisfied in order to make the diagnosis based upon the World Health Organization (WHO) guidelines shown in Table 1¹⁻³.

WHO divides SM into several categories, of which SM-AHNMD is one. Any AHNMD discovered in the presence of SM must be considered secondary to SM as opposed to *de novo*. Stratified as high-risk AML, the majority of patients are treated with

high-dose chemotherapy and stem cell transplant. To diagnose the two ailments concurrently requires WHO criteria to be met for both SM and AHNMD separately. More often in AML, the KIT mutation is present only on mast cells leaving blast cells vacant of the mutation, as opposed to other SM-AHNMD which may illustrate the mutant on both mast and blast cells⁴. Median survival usually ranges from 11–24 months^{5,6}. Poor prognostic factors include: (1) age ≥ 65 ; (2) anemia and thrombocytopenia; (3) weight loss and hypoalbuminemia; and (4) excess bone marrow blast cells ($>5\%$)⁵.

Differential diagnoses for the patient's diarrhea include other reasons for mast cell hyperplasia within the bone marrow like myelodysplastic syndromes, Hodgkin's and non-Hodgkin's lymphoma. The mast cell morphology in these cases would be normal with-

Table 1. WHO diagnostic criteria for systemic mastocytosis (modified from Valent et al.)³.

Major criterion	Multifocal dense infiltrates of mast cells (>15 mast cells in aggregates) in bone marrow biopsies and/or in sections of other extracutaneous organ(s)
Minor criterion	<ul style="list-style-type: none"> (a) >25% of all mast cells are atypical cells on bone marrow smears or are spindle-shaped in mast cell infiltrates detected on sections of visceral organs. (b) C-kit point mutation at codon 816 in the bone marrow or other extracutaneous organ. (c) Mast cells in bone marrow or blood or another extracutaneous organ express CD2 or/and CD25. (d) Serum tryptase concentration >20 ng/ml (this criterion only valid if an unrelated myeloid neoplasm has been excluded).

out mast cell aggregates, and bone marrow mast cells would display normal immunophenotypes lacking CD2 and CD25^{2,7,8}.

Zollinger-Ellison (ZE), carcinoid syndrome, and VIPoma are additional considerations for the cause of her diarrhea. These disorders present with flushing associated with sweating and absence of rash, hepatosplenomegaly. In SM, pigmentosa urticaria is common and hepatosplenomegaly can be seen in 20% of patients. VIPoma is diagnosed via vasoactive intestinal polypeptide (VIP) levels, ZE presents with gastrinemia, and urinary 5-hydroxyindoleacetic acid (5HIAA) is seen with carcinoid syndrome. These levels are all normal in SM⁹.

Management of SM remains intricate. Several studies have shown promising data with regard to curing the disease, but treatment frequently remains symptomatic due to the refractory nature of the mast cells to most conventional antineoplastic agents⁴. GI symptoms are present in anywhere from 60–80% of SM cases⁹. Abdominal pain affects approximately half of those with GI complaints, while diarrhea is common in 40%. Nausea and vomiting occur in 30% of these cases^{7,9}. While the majority of these symptoms are non-lethal, they are capable of severely affecting patients' quality of life.

Interferon-alfa provides relief of numerous symptoms, but it is poorly tolerated and long-term therapy is required^{5,10}. Cladribine (2-chlorodeoxyadenosine) recently showed promise as an effective cytoreductive agent providing a rapid decrease of mast cell infiltration and activation as well as symptomatic relief. But bone marrow suppression and mutagenic effects were the main adverse effects of cladribine¹⁰. The KIT mutation plays a significant role in treatment as the AML blast cell KIT mutant confers resistance to certain drugs, such as imatinib⁴.

Symptomatic treatment historically involves H1 and H2 histamine receptor blockers, ketotifen, cromolyn sodium, and anti-leukotriene drugs². Antihistamines relieve symptoms of flushing and pruritus and, by

decreasing gastric acid secretion, reduce diarrhea and abdominal cramping. Sodium cromolyn inhibits degradation of mast cells thus reducing the amount of mediators released and improving GI symptoms, especially diarrhea. Montelukast has been shown to relieve pruritus and flushing but may increase abdominal cramping⁷. Budesonide and other oral corticosteroids have proven effective in relieving abdominal pain and diarrhea⁹.

Our patient was treated with 50 mcg intravenous octreotide every 8 h due to the unavailability of oral sodium cromolyn at our facility and her concurrent AML precluded the use of corticosteroids for fear of further weakening her immune system. Octreotide provided significant symptomatic relief from diarrhea and greatly improved her quality of life. Only one other study was found to have attempted the use of octreotide in symptomatic relief of SM. Octreotide and total parental nutrition were successfully utilized to treat the patient's diarrhea and malnutrition due to SM¹¹.

Octreotide is a somatostatin analog, working by inhibiting serotonin release, secretion of gastrin, VIP and other hormones; it also decreases the rate of gastric emptying, smooth muscle contractions and splanchnic blood flow¹². It is indicated for diarrhea associated with VIPomas and carcinoid tumors as well as unlabeled uses for diarrhea resulting from chemotherapy and graft versus host disease. As a result of these two cases and octreotide's proven benefit in other conditions associated with significant diarrhea, we promote the option of octreotide as a viable alternative in the case of unavailability of sodium cromolyn and inability to use corticosteroids.

Further studies are highly recommended on the effective nature of this drug for its use in patients with SM. Comparison studies should be done to determine if it is as effective, or possibly more effective, in preventing or reducing diarrhea associated with SM. Limitations on this report include the age, medical comorbidities and complication with *C. diff* colitis and its possible effect on the course of our patient's diarrhea.

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